REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks that follow.

The foregoing amendment to the specification adds a cross-reference to the parent and grandparent applications. Applicants appreciate the Examiner's drawing their attention to this unintentional omission. A Petition to accept this delayed claim under 35 U.S.C. § 120 is filed herewith, together with the requisite fee.

The acknowledgment of the claim for foreign priority and of the certified copy of the priority document is noted, with appreciation.

Claims 21-28 are now in this application. Claims 1-20 have been canceled in compliance with the restriction requirement. Applicants of course reserve the right to file one or more divisional or other continuing applications directed to the canceled subject matter. All of Claims 21-28 read on the elected Group II invention. Claims 23-28 are directed solely to the elected species.

Claim 21 has been amended to incorporate therein the definition of the compounds located in original Claim 1, now canceled, from which Claim 21 previously depended. Claim 21 has been further amended to correct the adamantyl portion of formula (I) in accordance with the original version in the application and to otherwise place the claim in better form.

Claim 22 has also been amended to place it in better form, and in particular to avoid double inclusion of some of the conditions listed therein. Corrections are in accord with pages 14-16 of the specification.

Claim 23 has been amended to correct the representation of the adamantyl portion of formula (I) and to obviate 35 U.S.C. § 112 issues raised by the Examiner.

Claim 24 has been amended to restyle it as an independent claim and to place it in better form. The previous inclusion of the clause "and mixtures thereof" at the end of the claim has been canceled as redundant in light of the wording at the beginning of the claim "at least one stilbene compound".

New Claims 25 and 27 depend from Claims 23 and 24, respectively, but specify that the dermatological condition comprises psoriasis, cutaneous atopy, respiratory atopy or gingival hypertrophy. New Claims 26 and 28 depend from Claims 23 and 24, respectively, but specify that the dermatological condition comprises cutaneous psoriasis, mucous psoriasis, ungual psoriasis, psoriatic rheumatism, eczema, respiratory atopy or gingival hypertrophy. Page 14, lines 22-29 of the specification notes that the conditions specified in Claims 25-28 are dermatological conditions which are inflammatory and/or immunoallergic keratinization disorders.

No new matter has been added to the specification or claims by the foregoing amendment.

Claims 21-24 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Specifically, the Examiner has stated that the instant method of prevention or treatment of a dermatological condition involving an inflammatory and/or immunoallergic component reaches out to an as yet unidentified keratinization disorder having an inflammatory and/or immunoallergic component, the description of which is not found in the specification.

Applicants respectfully disagree with the Examiner's position and submit that all of Claims 21-28 are free of this rejection.

To begin with, it is pointed out that none of the claims now encompasses prevention, and that all of Claims 22 and 25-28 are limited to specific dermatological conditions and thus do not contain the rejected language (except by dependency, in which case they cannot be properly rejected but only objected to). Claim 21 also does not contain the language singled out by the Examiner. Claims 23 and 24 are now directed to a method for the treatment of a dermatological condition comprising an inflammatory and/or immunoallergic keratinization disorders. With respect to Claims 23 and 24, it is submitted that applicants are not required to disclose every conceivable embodiment of their invention to meet the written description requirement. Applicants have disclosed in the specification, for example, on page 14, a reasonable number of conditions falling within the language of Claims 23 and 24. That is all that is required. Withdrawal of the rejection is believed to be in order and is earnestly solicited.

Claims 21-24 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as their invention. It is submitted that all of Claims 21-28 are free of this rejection.

The 35 U.S.C. § 112, second paragraph, rejection is based on the use of the terms "involving" and "having an inflammatory and/or immunoallergic component". It is submitted that one of ordinary skill in the art would be well-aware of the meaning of the original language. Moreover, neither the word "involving" nor the expression "having an inflammatory and/or immunoallergic component" now appears in any of

the instant claims, rendering this rejection moot. While not agreeing that the original language was unclear, applicants submit that the new language of Claims 23 and 24 is clear and definite. Still, further, as pointed out above, all of Claims 22 and 25-28 are limited to specific dermatological conditions and thus do not contain any portion of the criticized language (except by virtue of their dependencies on Claims 23 and 24, in which case they cannot be properly rejected but only objected to). Withdrawal of the 35 U.S.C. § 112, second paragraph, rejection is believed to be in order and respectfully solicited.

Claims 21-24 have also been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirements. Applicants submit that all of the claims now in this application are fully enabled, i.e. that the specification describes the invention in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the invention.

The invention as claimed in Claims 23 and 24 is drawn to a method for the treatment of a dermatological condition comprising an inflammatory and/or immunoallergic keratinization disorder comprising administering to a patient in need of such treatment, an effective amount of at least one stilbene compound (as defined in the claim). This is the nature of the invention. None of the claims now reads on prevention. Moreover, none of the claims specifies that the compound must have affinity for "the retinoid receptor", contrary to what is indicated by the Examiner. The Summary of the Invention on pages 1-5 of the specification and the specific compounds of the invention taught on pages 7-10 of the specification, teach utility of the compounds in the claimed method without requiring that the use be linked to

affinity to a particular receptor. This issue will be discussed in more detail below in relation to the state of the art.

In summarizing the state of the art, the Examiner has stated that retinoid receptors have two major families designated RAR and RXR, which have different subtypes and tissue distributions. This is true. However, it is also known in the art that retinoids exist "which are biologically active without binding to retinoid transport proteins and to specific nuclear receptors"; see the Orfanos et al. article relied upon by the Examiner, page 361. The Charpentier et al. article relied upon by the Examiner notes on page 4993:

> Many biological effects of retinoids are mediated by activation of nuclear receptors (RARs) which are ligand dependent genetranscription factors.

Note the authors refer to many, not all, biological effects. Further, on page 4999, Charpentier et al. state:

> Studies have shown that RARs alone do not mediate the biological responses of retinoids. A key role for RXR as a dimer partner with RARs and the presence of different profiles of cognate hormone response elements in the target cell genes could be major factors influencing retinoid action and potency.

The Examiner, in further discussing the state of the art, notes that compounds "similar to retinoids having retinoid-like activity have been described" in the Charpentier et al. article. However, strictly speaking, it is clear from Orfanos et al. as well as Charpentier et al., that Charpentier et al.'s compounds are considered in the art to be retinoids, not just similar to retinoids. These compounds have retinoid-type activity. Charpentier et al.'s compounds are of course synthetic retinoids, not natural retinoids.

In further discussing the state of the art, the Examiner states that a retinoid receptor antagonist compound would counteract the retinoic acid effects, and relies on the Apfel et al. article as support for her position. This is not an accurate conclusion to draw from a thorough reading of Apfel et al. and is moreover contradicted by the Charpentier et al. article relied upon by the Examiner.

With respect to Apfel et al., the following excerpt from page 7129 clearly shows that the conclusion drawn by the Examiner is erroneous:

> We have also found retinoids with selective binding to RARα that are not competent to activate the receptor in a transactivation assay. We describe here one such retinoid, which prevents RARα activation by RA, thus displaying the characteristics of a RARα-selective antagonist. The retinoid counteracts RA effects in some but not other functional system. (Emphasis added).

Thus, according to Apfel et al. themselves, their retinoid receptor antagonist does not counteract retinoic acid effects across the board, but only in some systems.

Charpentier et al. also contradict the Examiner's conclusion. Two of the compounds reported there, **2** and **15**, were tested as antagonists in the F9 cell differentiation test and one of these, compound **15,** exhibited antagonist activity (IC_{50}=700±125). Yet compounds **2** and **15** exhibited moderate and high affinities for RARγ, respectively, while they were both inactive when tested for their ability to induce differentiation of F9 cells as estimated by plasminogen activator (PA) secretion. Compound **15** also showed RARα binding affinity and high RARβ binding affinity. Thus, it is clear that a retinoid can exhibit antagonist activity in the model described in instant Example 25 while still having binding affinity to RARs. Again, as noted by Apfel et al., an antagonist counteracts only some, not all, retinoic acid effects. The conclusion drawn by the Examiner is thus not supported by the art.

The Examiner further notes that while some retinoids have been shown to be useful for the treatment of psoriasis and several other keratinization disorders, the effect is unsatisfactory for treating other keratinerization disorders, such as inflammatory linear verrucous epidermal naevi and pachyonychia congenita. However, these are fairly rare conditions, the former being a birthmark arising from a defect in the ectoderm, the outer layer of the embryo that gives rise to epidermic and neural tissues, and the latter being a rare form of hereditary palmoplantar keratoderma of which there are only a few reports in the United States. Further, it is not indicated by Orfanos et al. which retinoids were administered, what dosage amounts and routes of administration were used, and what the size of the study was. Thus, what Orfanos et al. teach regarding these conditions in a review article published more than seven years ago cannot lead to a conclusion that no retinoid can be used to treat such conditions. Further, even if certain rare keratinization disorders could not be satisfactorily treated with a compound of the present invention, and even if such disorders were therefore be considered as inoperative species, there is no requirement that applicants' genus (a dermatological condition comprising an inflammatory and/or immunoallergic keratinization disorder) must exclude every possibly inoperative species. Still further, it is pointed out that the conditions questioned by the Examiner are not even encompassed by any of Claims 25-28.

The Examiner has further indicated that the criteria for predicting who is at risk of developing conditions of the type here claimed have not been established and the prevention of these conditions has not been shown. However, in order to expedite

prosecution, a method of prevention is no longer encompassed by the claims, rendering this point moot.

The Examiner has acknowledged that the level of skill in the retinoid art is high. We concur.

Nevertheless, the Examiner believes that there is a well-recognized degree of unpredictability in the retinoid receptor art. As proof of this, the Examiner cites Charpentier et al. With all due respect, applicants submit that the Examiner is overreacting to the teachings of Charpentier et al. A strict correlation of affinities and activities and structures is not what is significant. Within any given genus, there is always variation in activities. Moreover, Charpentier et al. describe 20 specific compounds, 19 of which show significant affinity and/or activity in one or more tests. That is 95% of the tested genus. As for the remaining single species, it is known only that it does not have binding affinity to RARα, RARβ or RARγ and that it is not active in the F9 differentiation test. This does not prove it is devoid of retinoid activity since, for example, nothing is said about RXR affinity or about other factors which can contribute to retinoid activity. What this in turn means is that one of ordinary skill can expect to find retinoid activity across a series. One need only resort to routine experimentation, subjecting a selected species to well-known tests for binding affinities and activity, to arrive at an affinity activity profile for a specific member of the genus. This is well within the skill in the art, which as the Examiner has acknowledged, is high.

The Examiner has indicated that there is no example in the specification of a compound wherein R' and R" are independently an amino acid, peptide or sugar residue. In order to expedite prosecution, these possible definitions of R' and R", as

well as these possible definitions of R_{12}, have been deleted from all of the claims. Therefore, this is no longer an issue herein.

The Examiner points out that the specification describes that the inventive compounds show activity in the test of differentiation of mouse embryonic teratocarcinoma cells (F9), and /or in the test of inhibition of ornithine decarboxylase after induction with TPA in mice. It is agreed that the specific results obtained are not included in the specification. However, literature citations are given for each test and the result that the compounds are active in one or both tests is indicated. Again, these are routine tests, a summary of the results is given, and there is no requirement in the patent law that specific results of biological tests must be included in a specification. Moreover, the fact that no *in vivo* procedures are described in the specification is unimportant; the Orfanos et al. and Charpentier et al. articles relied upon by the Examiner both show that the studies used by applicants in testing their compounds or similar studies are accepted in the art as showing retinoid activity.

Specifically regarding the procedure for assessing the RAR antagonist activity described in Example 25 (showing results for compounds of Examples 2, 4, 5, 10 and 7), it is pointed out that Example 25 is consistent with page 13, lines 13-15 of the specification, which indicates that some of the compounds of the invention are active in this test, not that all of them are. As noted on page 13 of the specification, this test dates from 1995, while the tests for which the results are summarized date from 1983 and 1978 and thus have been in use longer. Moreover, since a limited number of the inventive compounds have antagonist activity, whereas they all showed activity in one or both of the other summarized tests, it is suitable to specifically identify these particular antagonist compounds. A similar test for antagonist activity

is described in the Charpentier et al. article, where only one of twenty compounds was found to have antagonist activity. Again, while no *in vivo* procedure is described, *in vitro* procedures are well accepted in this art.

With respect to breadth of the claims and the Examiner's criticism of the structural diversity in the compounds of formula (I), it has already been pointed out that amino acid, peptide and sugar residues have been canceled from the claims. As to the polyhydroxyalkyl variation, it is not understood why this is considered so structurally remote from alkyl at this position, which is in fact specifically exemplified.

As to the Examiner's point about the antagonist compounds in the claims, it is again pointed out that the specification also teaches that these same compounds have agonist activity in that they are active in one of the two long-established tests cited earlier in the specification. And, as was pointed out earlier in this response, the art relied upon the Examiner clearly supports applicants' position that antagonist activity does not preclude retinoid activity. As was shown with respect to the Charpentier et al. article, the only antagonist therein has a high affinity for the RARγ receptor. Indeed, it is believed that the point of identifying antagonist activity has been misunderstood by the Examiner; such a compound, according to Apfel et al., page 7129, can be used to dissociate the multiple effects of retinoids "so as to obtain the described beneficial effects while limiting the unwanted side effects." Thus the second, fourth, fifth, seventh and tenth compound in Claim 24, i.e. the compounds of Examples 2, 4, 5, 7 and 10, which show antagonist activity, can indeed be used in the claimed method of treatment. Note in fact Formulation Example (1)(c), where a formulation of the compound of Example 4 is described for the treatment of psoriasis. Thus, the specification clearly teaches that the instant antagonist

compounds also have retinoid activity and can be used to treat keratinization disorders of the type here claimed.

It is clear from the foregoing that the specification contains sufficient teachings and guidance to allow one of ordinary skill to use all of the compounds as not claimed in the method of treatment as now claimed.

In view of the above, it is believed that the specification and the claims now in this application are free of all record rejections. Further, favorable action in the form of a Notice of Allowance is believed to be next in order and is earnestly solicited.

Respectfully submitted,

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Date: October 26, 2004

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